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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,625	07/16/2003	Steven Dell	4-32591A	9679
1095	7590	03/24/2004	EXAMINER	
THOMAS HOXIE NOVARTIS, CORPORATE INTELLECTUAL PROPERTY ONE HEALTH PLAZA 430/2 EAST HANOVER, NJ 07936-1080			WRIGHT, SONYA N	
			ART UNIT	PAPER NUMBER
			1626	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	10/620,625		DELL ET AL.	
	Examiner		Art Unit	
	Sonya Wright		1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>0304</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-23 are pending in this application.

Election/Restrictions

The Markush group set forth in the claims includes both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. This application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, each of these inventions contains a plurality of patentably distinct compounds, also far too numerous to list individually. Due to the numerous variables and their widely divergent meanings, a precise listing of inventive groups cannot be made. **For this reason, restriction is required under 35 U.S.C. 121.** An illustration of different inventive concepts may be made by reference to the compounds in the Examples of the instant application, as for example the compounds of:

- I. Example 1,
- II. Example 2,
- III. Example 3,
- IV. Example 4,
- V. Example 5, etc.

The Markush group claimed encompasses a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the other member(s) obvious under 35 U.S.C. 103.

An election of a single compound (or set of compounds) is required including an exact definition of each substitution on the base molecule (Formula I), wherein a single member at each substituent group or moiety is selected. For example, if a base molecule has a substituent group X, and X is defined to be any of methyl or benzyl, then applicant must select a single substituent of X, for example methyl, and each subsequent variable position. In the instant case, upon election of a single compound (or set of compounds), the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar thereto as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim which fall into the same class and subclass as the elected compound (or set of compounds), but may also include additional compounds which fall in related subclasses. Examination will then proceed on the elected compound AND the entire scope of the invention encompassing the elected compound. A clear statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits. Note that the restriction requirement will not be made final until such time as applicant is informed of the full scope of compounds along with process of using said compound under examination. This will be set forth by reference to specific class(es) and subclass(es) examined. Should applicant traverse on the ground that the compounds are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the compounds to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other.

All compounds falling outside the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to nonelected subject matter and will be withdrawn from consideration under 35 U.S.C. 121 and 35 C.F.R. 1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. 121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Markush claims must be provided with support in the disclosure for each member of the Markush group. See MOEO 608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Invention Set listed above is directed to or involves the use or making of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP 806.04, MPEP 808.01). Additionally,

the level of skill in the art is not such that one invention would be obvious over either of the other inventions, i.e. they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holdings of *Application of Papesch*, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and *In re Lalu*, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Mrs. Paivi Kukkola, Applicant's representative, on March 12, 2004, a provisional election was made with traverse to

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prosecute the invention of the species of Example 1. Affirmation of this election must be made by applicant in replying to this Office action. Claims withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

In view of Applicants' species election, the following generic embodiment has been identified for examination: a method for the preparation of indole derivatives of the formula (I) wherein, in formula (I), X is methyl; R1 and R2 are independently hydrogen or optionally substituted alkyl, R3 is halogen, and R4 is as defined. The remaining subject matter of claims 1-23 is withdrawn from further consideration under 37 CFR 1.142(b) as constituting other patentably distinct inventions.

The withdrawn subject matter of claims 1-23 is properly restricted as said subject matter differs in structure and element from the elected subject matter so as to be patentably distinct therefrom, i.e. a reference which anticipated the elected subject matter would not even render obvious the withdrawn subject matter and fields of search are not co-extensive.

Claim Objections

Claims 1-23 are objected to as containing non-elected subject matter. This objection may be overcome by limiting the claims to the elected subject matter identified supra.

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

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F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 4, 6, and 17-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-12 of U.S. Patent No. 6,596,877, Shieh et al.. Although the conflicting claims are not identical, they are not patentably distinct from each other because Shieh et al. embraces the subject matter of instant claims 1, 2, 4, 6, and 17-20. Shieh et al. teach the indole derivatives of formulas I and II in the instant claims by teaching an N-methyl heteroaromatic compound and an NH-containing heteroaromatic compound in claim 1 of the patent. Shieh et al. teach the use of dimethyl carbonate and of a base (catalyst) in claim 1 of the patent. Shieh et al. teach temperatures in claims 10-12 of 10°C to about 300°C, 80°C to about 200°C, and 90°C to about 160°C. The temperatures in claims 10-12 of Shieh et al. fall within the range of ambient temperature as defined in the instant specification. (In the instant specification, ambient temperature is defined on page 6, lines 15 and 16 to be 80°C to about 100°C for N-methylation reactions.) Shieh et al. teaches the use of a solvent, as in instant claims 17-20, in column 4, lines 50-54.

Shieh et al. provide motivation for the instant invention in the generic teaching in column 1, lines 66 and 67, and column 2, lines 1-6. Shieh et al. teach a NH-containing

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heteroaromatic compound and an N-methyl heteroaromatic compound in column 3, lines 1-23, for example. In column 3, lines 14-17, Sheih et al. indicate that substituents on the NH-containing heteroaromatic compound include but are not limited to, alkyl, alkenyl, aryl, (cycloalkyl)alkyl, arylalkyl, cycloalkyl, and halogen. In column 2, lines 4 and 5 Shieh et al. mention the base 1,4-diazabicyclo[2.2.2]octane which is disclosed in instant claim 2. Shieh et al. give preferred temperatures in column 4, lines 27-36 (10°C to about 300°C, 80°C to about 200°C, and 90°C to about 160°C), which fall within the range of the ambient temperatures defined in the instant specification (80°C to about 100°C). Shieh et al. provides examples of solvents in column 4, lines 50-54, and Shieh et al. specifically list dimethylformamide as an example of a solvent in column 4, line 51, as in instant claims 17-20. Therefore, the instant invention is suggested by Shieh et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

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3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,326,501, Jiang.

Determination of the scope and content of the prior art (MPEP §2141.01)

Applicant discloses a process for the preparation of indole derivatives of the formula (I) comprising reacting indoles of formula (II) with dimethyl carbonate when X is methyl in the presence of a catalytic amount of a base at an ambient temperature. Jiang teach a method for preparing indole derivatives comprising reacting an indole derivative with dimethyl carbonate in the presence of a suitable base or catalyst at ambient pressure. See Jiang, column 3, lines 66 and 67, and column 4, lines 1-45.

Jiang teaches the indole starting material of formula (II) in the instant claims in column 11, Example 7, wherein a 5-bromoindole starting material is used.

Jiang teaches the use of dimethyl carbonate as in the instant claims, in Example 7.

Jiang teaches the use of a base as in the instant claims, in Example 7, where potassium carbonate is used.

Jiang teaches that the reaction is performed at $\sim 130^\circ$, which differs from the ambient temperature taught in the instant claims.

Jiang teaches a molar ratio of base to indole starting material in Example 7 which differs from the molar ratios given instant claims 3 and 5. The molar ratios in instant claims 3 and 5 are 0.01:1 to 0.5:1 and 0.05:1 to 0.15:1.

Jiang teaches a methylated indole product, as in instant claim 4, wherein X is methyl. See the product of Example 7.

Jiang teaches an organic solvent, as in instant claims 7, 8, and 9 in Example 7, wherein N,N-dimethylformamide is used.

Jiang performs the reaction in Example 7 at a temperature of $\sim 130^\circ$, while instant claims 6 and 10 provide specific temperatures for the reaction, i.e, 80°C to 100°C and 90°C to 95°C .

Jiang teaches the use of tetrabutylammonium bromide in column 4, line 67 and column 5, lines 1-2. Therefore, Jiang teaches the ionic liquid mentioned in claim 11, but Jiang differs from the ionic liquid mentioned in claim 12.

Jiang teach a process which is similar to the instant process, when, in the instant claims, X is methyl, R1 and R2 are hydrogen or alkyl, R3 is halogen, and R4 is hydrogen or alkyl.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Regarding instant claim 1, the difference between Jiang and the instant claims is that in Example 7 of Jiang, the reaction was performed at a higher temperature than the temperature disclosed for the instant invention. In Example 7 of Jiang, the reaction was heated to a temperature of $\sim 130^\circ$, while in the instant claims, the reaction was performed at an ambient temperature, which is defined in the instant specification on page 6, lines 15 and 16 to be 80°C to about 100°C for N-methylation reactions.

Instant claims 3 and 5 provide specific mixture ranges for the molar ratio of the base to the compound of formula II initially present in the reaction mixture, i.e. 0.01:1 to 0.5:1 and 0.05:1 to 0.15:1. However, the molar ratio of the base to the indole starting material in Example 7 of Jiang differs from the molar ratio in the instant claims.

Instant claims 6 and 10 provide specific temperatures for the reaction, i.e, 80° C to 100°C and 90°C to 95°C. However, as mentioned supra, in Example 7, Jiang performs the reaction at a temperature of ~130°.

Instant claims 11 and 12 provide the limitation of an ionic liquid to be used in the instant process. Claim 12 limits the ionic liquid to tetra-n-butylammonium chloride. In column 4, line 67 and column 5, lines 1-2 Jiang teach the use of tetrabutylammonium bromide.

Finding of prima facie obviousness---rational and motivation (MPEP §2142-2143)

However, regarding the difference in temperature of the instant process and the process of Jiang, it is obvious to modify ranges such as temperature and mole ratios to optimize results. Changes in temperature, concentrations, or other process conditions of a known process do not impart patentability unless the recited ranges are critical, i.e. they produce a new and unexpected result, In re Aller et al., (CCPA 1955) 105 USPQ 233. A discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art, In re Boesch, (CCPA 1980) 205 USPQ 215.

Further, Jiang teaches that the reaction temperature may be modified in column 5, lines 49-52, where Jiang indicates that "The choice of reaction temperature is readily determinable by the skilled artisan. The reaction temperature will normally be above the boiling point of the reagent, around 90°C".

Instant claims 11 and 12 provide the limitation of an ionic liquid, and claim 12 limits the ionic liquid to tetra-n-butylammonium chloride. Jiang teach

tetrabutylammonium bromide, which teaches the ionic liquid of instant claim 11, but differs from the ionic liquid in claim 12 by bromide. However, it is obvious to substitute the anion chloride in instant claim 12 for bromide in Jiang, absent a showing of unexpected results.

Further, Jiang teaches homologs and isomers of the instant compounds of formulas I and II. Nothing unobvious is seen in substituting the known claimed isomer for the structurally similar isomer, as taught by Jiang, since such structurally related compounds suggest one another and would be expected to share common properties absent a showing of unexpected results. In re Norris, 84 USPQ 458 (1950). One of ordinary skill in the art would be motivated to use the teachings of Jiang to prepare the instant compounds in the expectation that positional isomers would be useful in the instant process.

Also, it is well established that the substitution of methyl for hydrogen on a known compound is not a patentable modification absent unexpected or unobvious results. In re Wood, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and In re Lohr, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963). The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (ie., usefulness in the instant process).

To those skilled in chemical art, one homolog is not such an advance over adjacent member of series as requires invention because chemists knowing properties of one member of series would in general know what to expect in adjacent members. In re Henze, 85 USPQ 261 (1950). The instant claimed compounds would have been

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obvious because one skilled in the art would have been motivated to prepare homologs of the compounds taught in the reference with the expectation of obtaining compounds which could be used in the instant process.

Therefore, the claimed process would have been suggested to one skilled in the art and the limitations of the instantly claimed subject matter of claims 4, 6, 7, 8, 9, 10, 11, 12 have been met by Jiang.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sonya Wright, whose telephone number is (703) 308-4539. The examiner can normally be reached on Monday-Friday from 8:00 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph K. McKane, can be reached at (703) 308-4537. The Unofficial fax phone number for this Group is (703) 308-7922. The Official fax phone numbers for this Group are (703) 308-4556 or 305-3592.

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Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [joseph.mckane@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees will not communicate with applicant via Internet e-mail where sensitive data will be exchanged or where there exists a possibility that sensitive data could be identified unless there is

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of record an express waiver of the confidentiality requirements under 35 U.S.C. 122 by the applicant. See the Interim Internet Usage Policy published by the Patent and Trademark Office Official Gazette on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-1235.


for Joseph K. McKane
Supervisory Patent Examiner
Group 1600

Sonya Wright

March 19, 2004